DOI:10.1111/hpb.12449 HPB

REVIEW ARTICLE

Delayed laparoscopic cholecystectomy increases the total hospital stay compared to an early laparoscopic cholecystectomy after acute cholecystitis: an updated meta-analysis of randomized controlled trials

Benjamin Menahem[1], Andrea Mulliri[1], Audrey Fohlen[2], Lydia Guittet[3], Arnaud Alves[1] & Jean Lubrano[1]

[1]Department of Digestive Surgery, University Hospital of Caen, Caen Cedex, France, [2]Department of Radiology, University Hospital of Caen, Caen Cedex, France, and [3]Cancers and Prevention Laboratory, Research Department, University Hospital of Caen INSERM U 1086, Centre François Baclesse, Caen Cedex, France

Abstract

Background: The objective of this study was to review the available prospective, randomized, controlled trials to determine whether an early (ELC) or a delayed (DLC) approach to a laparoscopic cholecystectomy is associated with an increase in length of hospitalization after acute cholecystitis.

Methods: Medline, the Cochrane Trials Register and EMBASE were searched for prospective, randomized, controlled trials (RCTs) comparing ELC versus DLC, published up to May 2014. A meta-analysis was performed using Review Manager 5.0.

Results: Nine RCTs were included in a total of 617 who underwent ELC and 603 patients who underwent DLC after acute cholecystitis. The mean hospital stay was 5.4 days in the ELC group and 9.1 days in the DLC group. The meta-analysis showed a mean hospital stay significantly lower in the ELC group [medical doctor (MD) = 3.24, 95% confidence interval (CI) = 1.95–4.54, $P < 0.001$]. The major biliary duct injury rate in the ELC group was 0.8% (2/247) and 0.9% (2/223) in the DLC group. The meta-analysis showed no significant difference between the ELC and DLC groups [relative risk (RR) =0.96, 95%CI = 0.25–3.73, $P = 0.950$].

Conclusion: DLC is associated with a longer total hospital stay but equivalent morbidity as compared to ELC for patients presenting with acute cholecystitis. ELC would appear to be the treatment of choice for patients presenting with ELC.

Received 24 February 2015; accepted 12 May 2015

Correspondence

Benjamin Menahem, Department of Digestive Surgery, University Hospital of Caen, Avenue de la Côte de Nacre, 14032 Caen Cedex, France. Tel: +33 231 065 020. Fax: +33 231 064 535. E-mail: benjamin.menahem@inserm.fr

Introduction

Acute cholecystitis is due to gallstones in up to 90% of patients. The reported prevalence of gallstones is up to 10% in adult Eastern populations and up to 15% in adult Western populations.[1] It is estimated that 20–40% of individuals with gallstones will develop associated symptoms, and 12% will develop acute cholecystitis.[2–4] A laparoscopic cholecystectomy is currently the gold standard treatment for symptomatic gallstone disease. However, the optimal timing of a cholecystectomy in patients with acute cholecystitis remains controversial. A laparoscopic cholecystectomy is usually delayed in these patients because of fears that early surgery may be associated with a higher rate of morbidity including post-operative bile leakage, and a higher rate of conversion to open surgery[5]. The updated Tokyo Guidelines suggest that an early laparoscopic cholecystectomy (ELC) is mandatory for patients with mild cholecystitis, whereas delayed laparoscopic cholecystectomy (DLC) can be performed in patients with moderate or severe cholecystitis.[5]

This aim of this meta-analysis was to review data from prospective randomized controlled trials (RCTs) that compared outcomes after ELC and DLC in patients with acute cholecystitis, to investigate the length of total hospital stay between these two approaches.

Methods

Data sources

A systematic review of the literature was performed. Articles published up to May 2014 by searching abstracts in Medline, the Cochrane database and Cochrane Clinical Trials Registry, and EMBASE, using the search terms [acute cholecystitis] AND [early] AND [delayed] AND [laparoscopic cholecystectomy] AND [random*] were identified. The search was limited to articles published in English. Two researchers independently searched for articles and compared their results. No unpublished data, data published in an abstract form only or non-full-length articles were included in the analysis.

Inclusion and exclusion criteria

Only prospective RCTs were included in this study. Laparoscopic cholecystectomy procedures performed for any reason were included. The search was limited to RCTs that compared outcomes after ELC and DLC in humans. The rates of post-operative bile leakage, major bile duct injury, conversion to open surgery, and overall morbidity, the presence or absence of postoperative drainage, the operative time and the total length of hospital stay were recorded. Observational studies, case reports and prospective studies were excluded.

Outcome definitions

The total length of hospital stay was defined as the total number of days in the hospital, which included two hospitalizations for patients who underwent DLC. Bile leakage was defined as bile detected in the drainage fluid or an intra-abdominal collection. A major bile duct injury was defined according to the Bismuth and Blumgart classification[6]. The intra-abdominal fluid collection was defined as detection of intra-abdominal fluid on post-operative ultrasonography or computed tomography.

Data review and extraction

Two researchers (B.M., J.L.) independently searched the databases; reviewed titles, abstracts and full-length articles; and selected articles to include in the analysis. The researchers also reviewed the reference lists of selected articles and previously published meta-analyses on the subject. Differences of opinion were resolved by consensus that included a third researcher (A.M.). The following information was extracted from the included studies: the date and design of the study; the number of patients who underwent ELC and DLC; the gender and age of patients and the number lost to follow-up; and the inclusion and exclusion criteria, outcome definitions, presence or absence of routine cholangiography, experience of the surgeons (consultant or trainee) and numbers of patients who received failed conservative treatment for acute cholecystitis. Missing data were requested from the authors of the relevant studies. The quality of the studies was determined using the Jadad scale.[7]

Statistical analyses

All statistical analyses were performed using Review Manager 5.0 software (Cochrane Collaboration, Oxford, UK). A fixed model was used if there was no evidence of heterogeneity, and otherwise a random effects model was used. Heterogeneity was assessed using the I^2 statistic, with values > 50% considered to indicate significant heterogeneity. Odds ratios (ORs) were calculated for each trial from the number of evaluable patients, and 95% confidence intervals (CIs) were calculated to confirm the effect size estimation and test criteria. The Mantel–Haenszel OR was calculated for dichotomous variables and the relative risk (RR) was calculated for rare events. The *P*-value for the overall effect was calculated using the Z test, with significance set at $P < 0.05$. Sensitivity analysis and estimation of publication bias were also performed.

Results

Trial characteristics

The process for selection of studies is shown in Figure 1. These nine studies that met inclusion criteria included 617 patients who underwent ELC and 603 who underwent DLC after acute cholecystitis[8–16]. The characteristics of these studies are shown in Table 1.

Results of meta-analysis

Total length of hospital stay

The total length of hospital stay was reported in all nine studies. The mean total length of hospital stay was significantly lower in patients who underwent ELC than in patients who underwent DLC (5.4 days versus 9.1 days; medical doctor (MD), 3.24; 95% CI, 1.95–4.54; $P < 0.001$) (Fig. 2).

Bile leakage

Post-operative bile leakage was reported in eight of the nine studies (1170 patients). The rate of bile leakage was significantly higher after ELC than after DLC (14/592, 2.4% versus 3/578, 0.3%; RR, 2.55; 95% CI, 1.05–6.20; $P = 0.041$) (Fig. 3).

Major bile duct injury

Major bile duct injury was reported in six of the nine studies (480 patients). The rate of major bile duct injury was not significantly different after ELC than after DLC (2/247, 0.8% versus 2/223, 0.9%; RR, 0.96; 95% CI, 0.25–3.73; $P = 0.950$).

Overall morbidity

Post-operative morbidity was reported in all nine studies. Overall morbidity was not significantly different after ELC than after DLC (91/617, 14.7% versus 129/603, 21.4%; OR, 1.04; 95% CI, 0.51–2.10; $P = 0.91$).

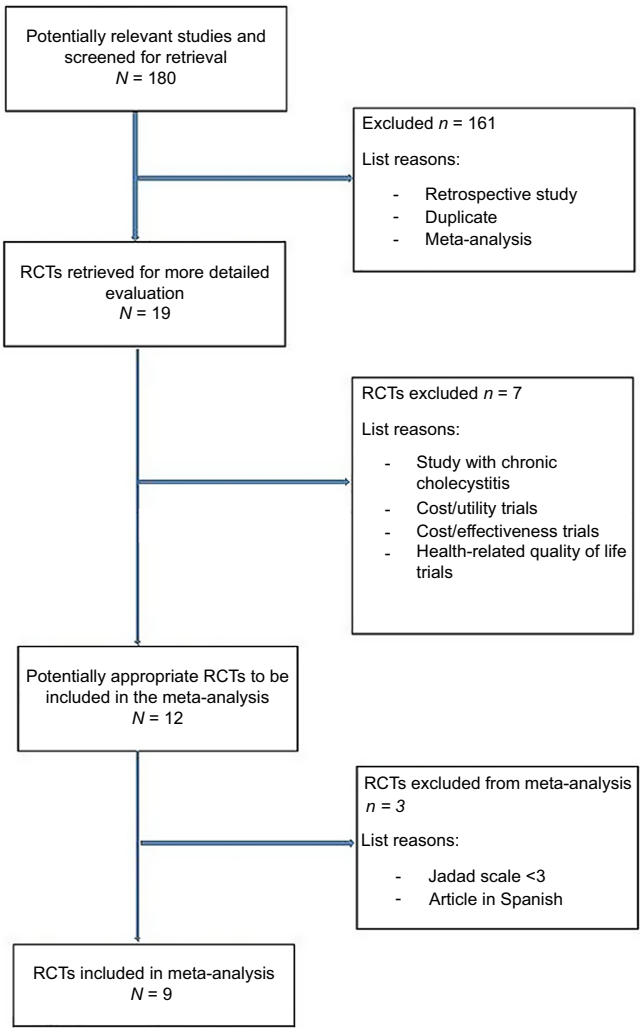

Figure 1 Flow-Chart of the meta-analysis

Intra-abdominal fluid collection

Post-operative intra-abdominal fluid collection was reported in five of the nine studies (998 patients). The rate of intra-abdominal fluid collection was not significantly different after ELC than after DLC (7/506, 1.4% versus 8/492, 1.6%; RR, 0.79; 95% CI, 0.31–2.06; $P = 0.63$).

Conversion to open surgery

Conversion to open surgery was reported in all nine studies. The rate of conversion was not significantly different after ELC than after DLC (86/617, 13.9% versus 84/603, 13.9%; RR, 0.97; 95% CI, 0.74–1.28; $P = 0.84$).

Operative time

The operative time was reported in seven of the nine studies (530 patients). The mean operative time was not significantly different between ELC and DLC (105 min versus 91 min; MD, 10.18; 95% CI, −1.48–21.85; $P = 0.09$).

Post-operative drainage

Post-operative drainage was reported in three of the nine studies (186 patients). Placement of an intra-operative drainage tube was significantly more frequent in patients who underwent ELC than in patients who underwent DLC (74/95, 77.8% versus 37.3%; OR, 6.18; 95% CI, 3.19–11.99; $P < 0.001$) (Fig. 4).

Sensitivity analysis and publication bias

Sensitivity analysis and publication bias estimation were performed to estimate statistically significant results. For overall morbidity, operative time and the total length of hospital stay, the combined OR (or MD) was calculated using both a fixed-effects and a random-effects model, and the results were compared.

Discussion

This meta-analysis of RCTs found that DLC was associated with a significantly longer total hospital stay and significantly lower rate of post-operative bile leakage than ELC in patients with acute cholecystitis. However, the rates of major bile duct injury, overall morbidity and conversion to open surgery, and the mean operative time, were not significantly different between ELC and DLC.

The choice of ELC versus DLC in patients with acute cholecystitis remains controversial, even although this issue has been investigated by randomized[8] and prospective studies.[17–20] All these previous studies concluded that the rates of post-operative complications and conversion to open surgery were similar after ELC and DLC. These results are also supported by a recent population-based study,[21] which found that ELC was associated with a shorter total hospital stay and a similar rate of post-operative complications compared with DLC.

Other previous studies have also reported on the total length of hospital stay.[31,32] The length of hospital stay and cost-effectiveness have become increasingly important in recent years. Some centres prefer to avoid DLC because it requires a second hospitalization, which increases the total length of hospital stay and is associated with a risk of recurrence of cholecystitis before surgery. As reported, there were some patients who underwent their surgery before the operative date in the DLC group (Table 1).

This meta-analysis has some limitations. First, the timing of ELC and DLC differed among studies. ELC was performed as soon as 24 h after admission in some studies,[8,11,15,16] at 48–72 h after admission in other studies,[9,10,12,14] and as late as 7 days after admission in the study by Yadav *et al.*[13] DLC was performed between 6 and 12 weeks after acute cholecystitis.

Analysis of the secondary outcomes of the study found that post-operative bile leakage was significantly associated with ELC. This differs from the findings of previous meta-analyses and RCTs. However, interpreting the significance of this result is difficult as the rates of post-operative drainage were signifi-

Table 1 Characteristics of studies included in the meta-analysis

Study (year, Country)	Number of patients (ELC/DLC)	Outcomes definition (according to TG 13 for AC)			Monocentre study	Consultant surgeon	Routinely cholangiography	Failure of conservative treatment
		AC	ELC	DLC				
Lai (1998, China)	53/38	Yes	Within 24 h of admission	6–8 weeks later	Yes	Yes	No	8
Lo (1998, China)	45/41	Yes	Within 72 h of admission	8–12 weeks later	Yes	Yes	No	8
Johansson (2003, Sweden)	74/69	Yes	Within 48 h of admission but no more than 7 days after the onset of the symptoms	6–8 weeks later	Yes	No	Yes	18
Kolla (2004, India)	20/20	Yes	Within 24 h of admission	6–12 weeks later	Yes	Yes	No	
Macafee (2009, United Kingdom)	36/36	Not detailed in the study	Within 72 h of admission	12 weeks later	Yes	No	Considered only necessary by surgeon	4
Yadav (2009, Nepal)		No	As soon as possible but until 7 days within admission	6–8 weeks later	Yes	Yes	NR	NR
Gul (2013, India)	30/30	Yes	Within 72 h of admission	6–12 weeks later	Yes	Yes	Not detailed in the study	Not detailed in the study
Gutt (2013, Germany)	304/314	Yes	Within 24 h of admission	Until 45 days after enrollment	No	Not detailed in the study	Not detailed in the study	Not detailed in the study
Ozkardes (2014, Turkey)	30/30	Yes	Within 24 h of admission	6–8 weeks later	Yes	No	Not detailed in the study	Not detailed in the study

AC, acute cholecystitis; DLC, delayed laparoscopic cholecystectomy; ELC, early laparoscopic cholecystectomy; US, ultrasound; TG 13, Tokyo Guidelines 2013 definition.

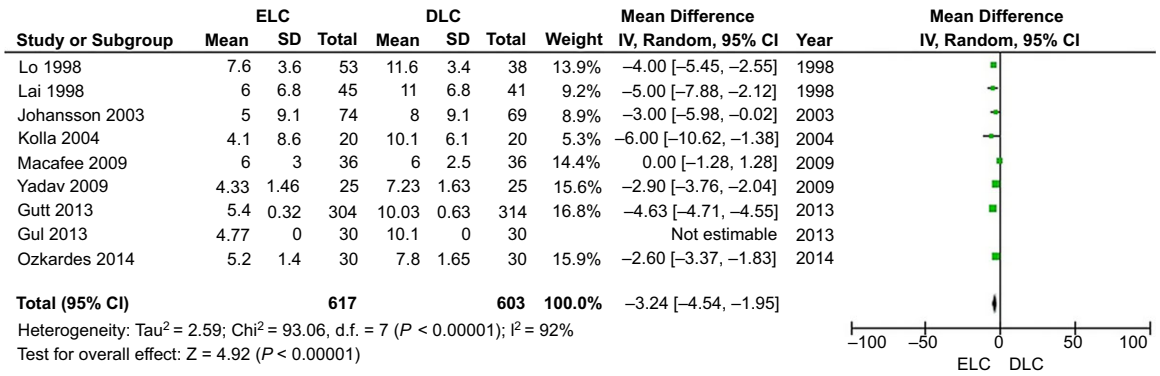

Figure 2 Meta-analysis of the total length hospital stay

cantly higher in the ELC group and, thus, may have influenced the reported incidence. Outcome data regarding morbidity or subsequent intervention would need to be reported to understand if this is significant.

Bile duct injuries are a major concern after a cholecystectomy and are divided into minor and major injuries according to the Strasberg classification.[22] After a laparoscopic cholecystectomy, the reported rate of minor bile duct injuries is 0.1–1.7%, and of major bile duct injuries is 0.1–0.9%. Obesity, peri-operative bleeding and local inflammation secondary to pancreatitis or acute cholecystitis are well-known risk factors for bile duct injury.[23,24] In patients with bile duct injuries, the right hepatic artery is also injured in 7–12% of patients.[25–30]

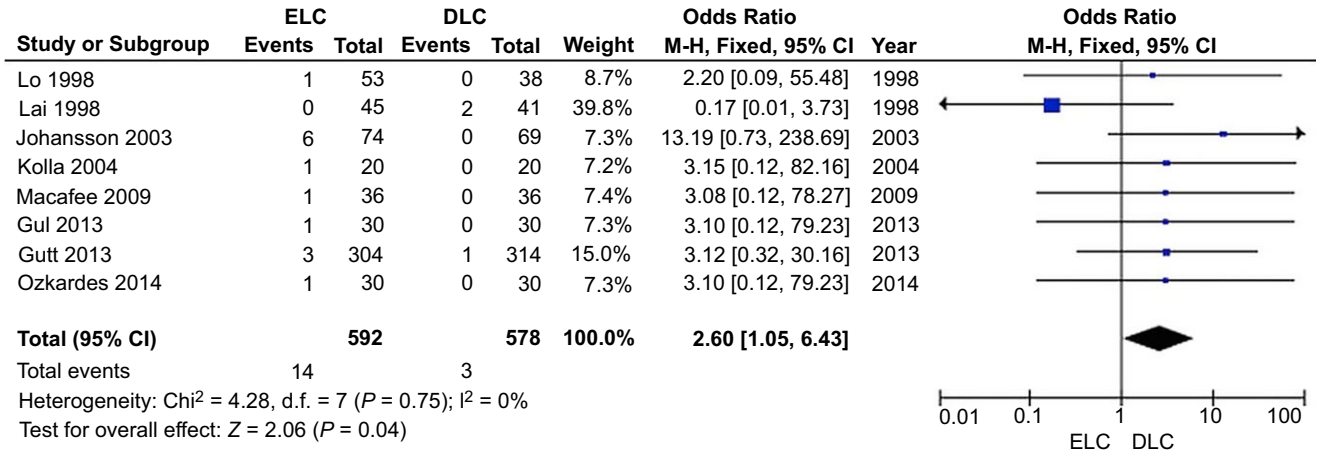

Figure 3 Meta-analysis of the post operative bile leakage

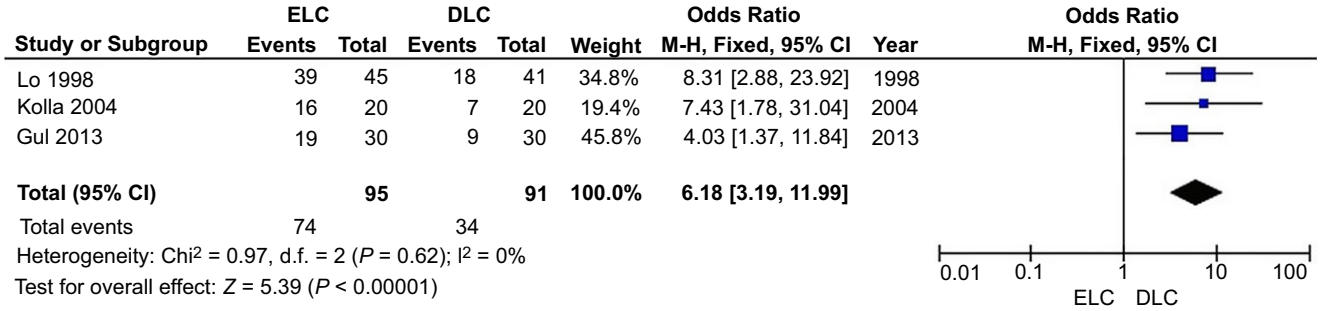

Figure 4 Meta-analysis of the post-operative drainage

The present findings that the rates of overall morbidity, major bile duct injury and mortality were not significantly different between patients who underwent ELC and DLC were consistent with the findings of four previous meta-analyses. However, Siddiqui *et al.*[31] found that ELC was associated with a longer mean operative time than DLC, which differs from the present findings.

The findings of recent studies suggest that ELC may reduce healthcare costs[33–35] and increase the quality of life[36,37] compared with DLC in patients with acute cholecystitis.

Conclusion

DLC is associated with a longer total hospital stay but equivalent morbidity as compared with ELC for patients presenting with acute cholecystitis. ELC would appear to be the treatment of choice for patients presenting with AC.

Acknowledgements

None.

Funding sources

Nothing to disclose.

Conflict of interest

None declared.

References

1. Gurusamy KS, Davidson C, Gluud C, Davidson BR. (2013) Early versus delayed laparoscopic cholecystectomy for people with acute cholecystitis. *Cochrane Database Syst Rev* 6:CD005440.
2. Stinton LM, Myers RP, Shaffer EA. (2010) Epidemiology of gallstones. *Gastroenterol Clin North Am* 39:157–159.
3. Portincasa P, Moschetta A, Palasciano G. (2006) Cholesterol gallstone disease. *Lancet* 368:230–239.
4. Portincasa P, Moschetta A, Petruzzelli M, Palasciano G, Di Ciaula A, Pezzolla A. (2006) Gallstone disease: symptoms and diagnosis of gallbladder stones. *Best Pract Res Clin Gastroenterol* 20:1017–1029.
5. Gomi H, Solomkin JS, Takada T, Strasberg SM, Pitt HA, Yoshida M *et al*. (2013) TG13 antimicrobial therapy for acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Sci* 20:60–70.
6. Bismuth H, Majno PE. (2001) Biliary strictures: classification based on the principles of surgical treatment. *World J Surg* 25:1241–1244.

7. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ *et al*. (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 17:1–12.
8. Lai P, Kwong K, Leung K, Kwok SP, Chan AC, Chung SC *et al*. (1998) Randomized trial of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Br J Surg* 85:764–767.
9. Lo CM, Liu CL, Fan ST, Lai EC, Wong J. (1998) Prospective randomized study of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Ann Surg* 227:461–467.
10. Johansson M, Thune A, Blomqvist A, Nelvin L, Lundell L. (2003) Management of acute cholecystitis in the laparoscopic era: results of a prospective randomized clinical trial. *J Gastrointest Surg* 7:642–645.
11. Kolla SB, Aggarwal S, Kumar A, Kumar R, Chumber S, Parshad R *et al*. (2004) Early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Surg Endosc* 18:1323–1327.
12. Macafee DA, Humes DJ, Bouliotis G. (2009) Prospective randomized trial using cost-utility analysis of early versus delayed laparoscopic cholecystectomy for acute gallbladder disease. *Br J Surg* 96:1031–1040.
13. Yadav RP, Adhikary S, Agrawal CS, Bhattarai B, Gupta RK, Ghimire A. (2009) A comparative study of early versus delayed laparoscopic cholecystectomy in acute cholecystitis. *Kathmandu Univ Med J (KUMJ)* 7:16–20.
14. Gul R, Dar R, Sheikh R, Salroo NA, Matoo AR, Wani SH. (2013) Comparison of early versus delayed laparoscopic cholecystectomy for acute cholecystitis: experience from a single center. *N Am J Med Sci* 5:414–418.
15. Gutt C, Encke J, Köninger J, Harnoss JC, Weigand K, Kipfmüller K *et al*. (2013) Early versus delayed cholecystectomy, a multicenter randomized trial (ACDC study, NCT00447304). *Ann Surg* 258:385–393.
16. Ozkardes AB, Tokac M, Dumlu EG, Bozkurt B, Ciftçi AB, Yetisir F *et al*. (2014) Early versus delayed laparoscopic cholecystectomy for acute cholecystitis: a prospective randomized study. *Int Surg* 99:56–61.
17. Pessaux P, Tuech JJ, Rouge C, Duplessis R, Cervi C, Arnaud JP. (2000) Laparoscopic cholecystectomy in acute cholecystitis. *Surg Endosc* 14:358–361.
18. Serralta A, Bueno J, Planells M,Rodero DR. (2003) Prospective evaluation of emergency versus delayed laparoscopic cholecystectomy for early cholecystitis. *Surg Laparosc Endosc Percutan Tech* 13:71–75.
19. Gonzalez-Rodriguez F, Paredes-Cotoré J, Ponton C, Rojo Y, Flores E, Luis-Calo ES *et al*. (2009) Early versus laparoscopic cholecystectomy in acute cholecystitis? Conclusion of a controlled trial *Hepatogastroenterology* 56:11–16.
20. Teckchandani N, Garg P, Hadke N, Jain SK, Kant R, Mandal AK *et al*. (2010) Predictive factors for successful early laparoscopic cholecystectomy in acute cholecystitis: a prospective study. *Int J Surg* 8:623–627.
21. De Mestral C, Rotsein O, Laupacis A, Hoch JS, Zagorski B, Alali AS *et al*. (2014) Comparative operative outcomes of early and delayed cholecystectomy for acute cholecystitis. A population-based propensity score analysis. *Ann Surg* 259:10–15.
22. Strasberg SM, Hertl M, Soper NJ. (1995) An analysis of the problem of biliary duct injury during laparoscopic cholecystectomy. *J Am Coll Surg* 180:101–125.
23. Schmidt SC, Langrehr JM, Hintze RE, Neuhaus P. (2005) Long-term results and risk factors influencing outcome of major bile duct injuries following cholecystectomy. *Br J Surg* 92:76–82.
24. Söderlund C, Frozanpor F, Linder S. (2005) Bile duct injuries at laparoscopic cholecystectomy: a single-institution prospective study. Acute cholecystitis indicates an increased risk. *World J Surg* 29:987–993.
25. Halasz NA. (1991) Cholecystectomy and hepatic artery injuries. *Arch Surg* 126:137–138.
26. Alves A, Farges O, Nicolet J, Watrin T, Sauvanet A, Belghiti J. (2003) Incidence and consequence of an hepatic artery injury in patients with postcholecystectomy bile duct strictures. *Ann Surg* 238:93–96.
27. Buell JF, Cronin DC, Funaki B, Koffron A, Yoshida A, Lo A *et al* (2002) Devastating and fatal complications associated with combined vascular and bile duct injuries during cholecystectomy. *Arch Surg* 137:703–708.
28. Mathisen O, Søreide O, Bergan A. (2002) Laparoscopic cholecystectomy: bile duct and vascular injuries: management and outcome. *Scand J Gastroenterol* 37:476–481.
29. Boerma D, Rauws EA, Keulemans YC, Janssen IM, Bolwerk CJ, Timmer R *et al*. (2001) Impaired quality of life 5 years after bile duct injury during laparoscopic cholecystectomy: a prospective analysis. *Ann Surg* 234:750–757.
30. Stewart L, Way LW. (2009) Laparoscopic bile duct injuries: timing of surgical repair does not influence success rate. A multivariate analysis of factors influencing surgical outcomes. *HPB* 11:516–522.
31. Siddiqui T, MacDonald A, Chong P, Jenkins JT. (2008) Early versus delayed laparoscopic cholecystectomy for acute cholecystitis: a meta-analysis of randomized controlled trials. *Am J Surg* 195:40–47.
32. Lau H, Lo C, Patil G, Yuen WK. (2006) Early versus delayed-interval laparoscopic cholecystectomy for acute cholecystitis. A meta-analysis. *Surg Endosc* 20:82–87.
33. Wilson E, Gurusamy K, Gluud C, Davidson BR. (2010) Cost-utility and value-of-information analysis of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Br J Surg* 97:210–219.
34. Dixon E, Fowler D, Ghitulescu G, Evidence Based Reviews in Surgery Group. (2012) Cost-utility analysis of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *J Can Chir* 55:204–206.
35. Johner A, Raymakers A, Wiseman S. (2013) Cost-utility of early versus delayed laparoscopic cholecystectomy. *Surg Endosc* 27:256–262.
36. Johansson M, Thune A, Blomqvist A, Nelvin L, Lundell L. (2004) Impact of choice of therapeutic strategy for acute cholecystitis on patient's health-related quality of life. Results of a randomized, controlled clinical trial. *Dig Surg* 21:359–362.
37. Morris S, Gurusamy K, Patel N, Davidson BR. (2014) Cost-effectiveness of early laparoscopic cholecystectomy for mild acute gallstone pancreatitis. *Br J Surg* 101:828–835.